



Phytosomes: A Promising Strategy for Enhanced Therapeutic Benefits of Phytochemicals

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ABSTRACT

Phytosomes are phytochemical based novel drug delivery systems that lead to better absorption, greater bioavailability in addition to improved therapeutic efficacy of numerous phytoconstituents. It is a supremely advanced form of herbal formulations which contains the active phytoconstituent of herbal extract bound by phospholipid molecule. Additionally, these also act as vesicular systems for various fascinating and significant phytoactive. The phytosomes technique produces remarkable minute spheres or tiny cells, which is helpful in the protection of active phytochemical constituent from destruction by the gastric environment. Furthermore, phytosomes also reveal efficient pharmacokinetic as well as pharmacodynamic profile compared to conventional herbal extracts. The current manuscript is a cogent attempt to review the potential pharmacological benefits of herbal extracts by forming an impressive and successful phytospholipid complex. Salient attributes, as well as promising and imperative applications of phytosomes, are illustrated in the manuscript. Recent advances in research endeavours, along with major inferences on effective phytosomal drug delivery systems, have also been highlighted.



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INTRODUCTION

Recently, the popularity of herbal formulations augmented extensively across the globe. The therapeutic efficacy of various pharmacological plant actives has been investigated by several researchers from

all over the world (Silva *et al.*, 2014). In recent years, approximately 30-45% of drug molecules are mainly obtained from natural origin (Talware *et al.*, 2018). Generally, herbal drugs have less toxic effects as compared to other synthetic medications (Kidd, 2009). Also, herbal plant actives may contribute a major avenue in the formulation of innovative clinically employed medicines on the basis of ethnopharmacological information (Talware *et al.*, 2018). Moderate solubility, as well as less bioavailability of various medicinal plant actives, creates an issue to deliver the biomedicine in the systemic circulation. For enhanced bioavailability, herbal actives should have an appropriate balance between hydrophilic (for dissolving into gastric fluid) and lipophilic (to cross the lipid biomembrane) (Semalty *et al.*, 2010). The partial and inaccurate absorption of phytoconstituents is due to the large structure of a polyphenolic compound, low

lipid compatibility and multiple rings present in it (Lu *et al.*, 2019). However, the most appropriate as well as pioneer strategy to transport botanical extracts is recognised as pharmaceutical nanotechnology (Babazadeh *et al.*, 2018). The nano-sized vesicles loaded with synthetic and herbal drugs have an outstanding acceptance for this well established approach. Wide ranges of 'somes' have been introduced like liposomes, niosomes, aquasomes, phytosomes, emulsomes, transferosomes, virosomes etc., to overcome complications of poor solubility (Pawar and Bhangale, 2015). The complex form of polar phytoactive constituents and phospholipid has been vastly prepared, which is prevalently known as phytosomes, to overcome the low systemic bioavailability of herbal extracts (Shakeri and Sahebkar, 2016). 'Phyto' means plant, and 'some' means cell like and they are indicated as herbosomes and phytolipid delivery system (Bhattacharya, 2009). Phytosomes (phospholipid vesicles) are used to deliver nutraceuticals, water-soluble herbal extracts and some large lipophilic molecules and also improve pharmacokinetic and pharmacodynamic profile (Talware *et al.*, 2018). Phytosome is a complex of phospholipid which enrolls the herbal extract inside it and prevents any enzymatic degradation (Alexander *et al.*, 2016). Phytosome helps to progress the drug molecules through the cell membrane and reach systemic circulation (Talware *et al.*, 2018). Phospholipids bound with phytoactive molecules can effortlessly reach their targeted site (Alexander *et al.*, 2016). Various types of phospholipid used for the preparation of phytospholipid complex includes phosphatidylcholine, phosphatidylserine, phosphatidic acid, phosphatidylinositol, phosphatidylglycerol etc., (Lu *et al.*, 2019). Phosphatidylcholine is generally utilized as a phospholipid in which the phosphatidyl part is lipophilic and the choline part is hydrophilic and can easily cross the membrane when it is given topically and also not degraded in gastrointestinal tract when ingested orally (Babazadeh *et al.*, 2018).

Salient Benefits

In terms of therapeutic efficacy, phytosomal preparations are recognised as superior and emerging vistas than conventional phytomedicines. In addition, phytosomes reveal greater physicochemical stability. Following are some pivotal advantages of phytospholipid complexes (Talware *et al.*, 2018; Alexander *et al.*, 2016).

The pharmacokinetic and pharmacodynamic profile of phytoextract can be improved by phytosomal formulation. It can be given orally as well as trans-

dermally. It helps to deliver large molecular active constituents. The dose frequency of the drug can be reduced. The chemical bond between the phytoconstituents with phosphatidylcholine imparts stability to the phytoconstituents. Phosphatidylcholine is an important complexing agent in phytosomes. It acts as a carrier in drug delivery and also provides the hepatoprotective activity. Unique physicochemical characteristics of phospholipids confer phytosomes an amphiphilic nature. It enhances the percutaneous absorption of phytoactive and also used in cosmetics. Some valuable phytomedicines can also be prevented from degradation in gastric fluid and gut bacteria. Phytosomes not only enhance the membrane permeability of hydrophilic phytoactive but also increase the solubility aspect of lipophilic polyphenols in the aqueous phase. Phytosomes are biocompatible and biodegradable delivery systems.

Limitations

Herbal extracts are accepted worldwide owing to fewer side effects and lesser cost, but their therapeutic efficacy is limited, which can be rectified with the help of phytosomes. However, phytosomal formulation has some limitations as follows (Babazadeh *et al.*, 2018).

1. pH sensitivity of phospholipids.
2. Sometimes, phytoconstituents from phytosomal preparation may rapidly extract out.

Significant attributes

In the Ayurvedic system, herbal preparations have been used for the therapy of various diseases, but it takes more time the treatment. Modern technology has been adopted in which the size of a drug molecule can be reduced and prevented from degradation. Important features concerning phytospholipid complexes are explained in the subsequent section (Pawar and Bhangale, 2015).

The size of the phytosome ranges from 50 nm to a few hundred μm . Phytosomal complex is formed by the chemical bond between the Phyto molecule and phospholipids. Phytosomes are frequently freely soluble in aprotic solvents, fairly soluble in fats, water insoluble and comparatively unstable in alcohol. Phyto-phospholipid interaction is owing to hydrogen bond formation between the polar functional group of phytomolecule and polar head of phospholipid (i.e., phosphate and ammonium group). They can be unilamellar/multilamellar depending upon hydration pattern. Phospholipids are prospective vehicles for improving the bioavailability of phytoactive molecules owing to their inim-

itable structural composition identical to the composition of the cell membrane, making them well-suited with physiological systems.

Procedure

Phytosomes are developed by the interaction of 2-3 moles (normally 1 mole) of phospholipid (as phosphatidylcholine, phosphatidylserine etc.) with 1-mole phytoconstituent. Different methods, such as antisolvent precipitation, co-solvent lyophilization, solvent evaporation etc., are commonly employed in phytosomal preparation (Babazadeh *et al.*, 2018), as shown in Figure 1.

Characterization and Spectroscopic Evaluation

The performance of phytosomal preparations are characterized by crucial attributes as shape, size, size distribution, entrapment volume, drug release percentage, chemical composition etc., as shown in Figure 2. The phytosomes are also evaluated by UV, Fourier-transform infrared spectroscopy, nuclear magnetic resonance spectroscopy, X-ray crystallography, differential scanning calorimetry, scanning electron microscopy, transmission electron microscopy etc., (Lu *et al.*, 2019).

Potential Applications

Phytosomal drug delivery confers various potential applications in order to overcome constraints associated with phytoconstituents. These beneficial applications have been summarized along with some important examples and are schematically represented in Figure 3.

Hepatoprotective features

Various phytophospholipid complexes represented promising action in the management of liver disorders, for example, silymarin phytosomes has shown efficient hepatoprotective potential (El-Gazayerly *et al.*, 2014). Ginkgoselect phytosome has also presented hepatoprotective effect in rifampicin induced hepatotoxicity (Naik and Vandana S. Panda, 2008), quercetin phytosomes exhibited enhanced therapeutic benefits in carbon tetrachloride induced acute liver toxicity (Maiti *et al.*, 2005), Andrographolide herbosome elicited better bioavailability along with improved hepatoprotective activity (Maiti *et al.*, 2010), luteolin phospholipid complex has been explored for hepatoprotective activity (Khan *et al.*, 2016). Mangiferin herbosomes have also been evaluated for hepatoprotective potential against ethanol induced hepatotoxicity (Jain *et al.*, 2013).

Anticancer potential

Numerous actives incorporated in phytosomal preparations exhibited efficient anticancer potency

for different cancers, such as silybin phytosomes are investigated in the management of prostate cancer (Flaig *et al.*, 2007) and luteolin-loaded nano phytosomes have been explored for human breast carcinoma (Sabzichi *et al.*, 2014). Silybin-phosphatidylcholine complex has shown antitumour activity against ovarian cancer (Gallo *et al.*, 2003) and the phytosome complex of *Terminalia arjuna* bark methanolic extract depicted antiproliferative activity on human breast cancer cell lines (Sharma *et al.*, 2015).

Miscellaneous activities

Phytosomal preparations have been studied for various other miscellaneous therapeutic activities such as acute cognitive effect has been investigated by utilizing phytosomal complex of Ginkgo biloba extract and phosphatidylserine (Kennedy *et al.*, 2007), resveratrol phytosomes presented anti-inflammatory effect (Kalita *et al.*, 2017), wound healing activity was explored by using *Wrightia arborea* as well as by sinigrin phytosomes (Devi and Divakar, 2012; Mazumder *et al.*, 2016a) and quercetin loaded nanophytosomes also elicited improved antioxidant potential (Rasae *et al.*, 2014).

Bioavailability enhancement

Phytosomal complexes are also explored for bioavailability enhancement of various herbal actives such as evodiamine phytosomes remarkably enhanced the oral bioavailability (Tan *et al.*, 2012). Bioavailability enhancement of nutraceuticals using phytosomal approach has also been studied (Bhattacharya, 2009). Salvianolic acid B pellets phytosome have shown enhanced permeability and bioavailability of drug (Li *et al.*, 2013).

Fitness management profile

Green select phytosome has been evaluated for weight maintenance (Gilardini *et al.*, 2016). Furthermore, thermogel of nanosized soy phytosomes have also been investigated for anti-obesity effect (El-Menshawe *et al.*, 2018).

Cosmetic applications

Phytosomes are gaining popularity in cosmetic technology. They are utilized in the preparation of various cosmeceutical products and ultimately help in enhancing the appearance and beauty aspects (Bombardelli, 1991). Phytosomal complex acts in many ways, exhibiting better photoprotective potential and effective antiaging property (Joshua *et al.*, 2018). Quercetin phytosomes have also been evaluated for interesting anti-itching and soothing effect (Maramaldi *et al.*, 2016).

Table 1: Recent research endeavours on phytosomes

S. No	Herbal extract/ Plant actives	Major findings	Reference (s)
1.	Naringenin	Treatment of acute lung injury	Yu et al. (2020)
2.	Hesperidin	Improved dissolution and bioavailability	Kalita and Patwary (2020)
3.	Escin β -sitosterol	Better antihyperalgesic activity	Djekic et al. (2019)
4.	Quercetin	Improved oral absorption and enhanced bioavailability	Riva et al. (2019)
5.	Rutin	Improved entrapment efficacy	Vu et al. (2018)
6.	Quercetin	Enhanced therapeutic efficacy	El-Fattah et al. (2017)
7.	Curcumin	Increased bioavailability	Mirzaei et al. (2017)
8.	Sinigrin	Increased in-vitro skin permeation	Mazumder et al. (2016b)

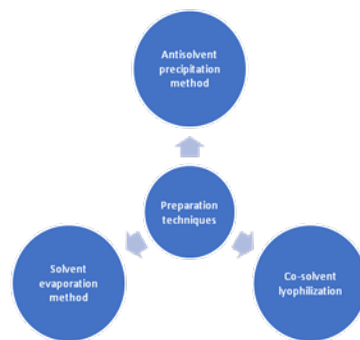


Figure 1: Different methods used for preparation of phytosomes

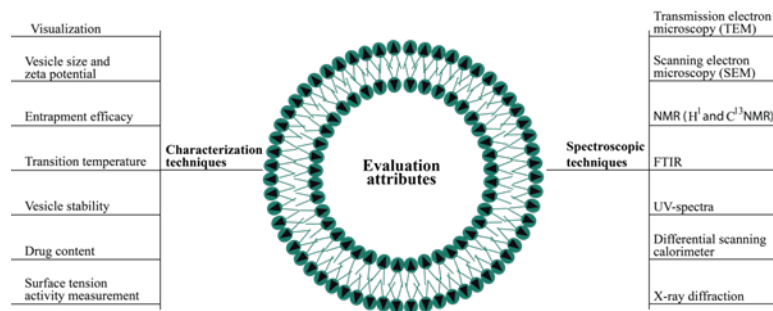


Figure 2: Schematic representation of various evaluation techniques

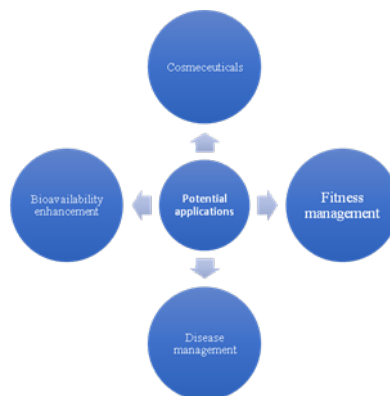


Figure 3: Unique applications of phytosomal preparations

Various significant innovations are being carried out on numerous herbal moieties and owing to phytophospholipid complex, enhancement in their therapeutic activity has been generally observed. Various phytosomal scaffolds of diverse herbal drugs developed by the scientific community globally, along with improved pharmacological activity, have been reported in Table 1.

Future Perspectives

Advancements and sophisticated research should be focused to accomplish the development of multitalented phytosomes for enhancing the bioavailability of phytoactive in a successful and efficient manner. Progress in synergistic as well as promising innovations of phytosomes employing superior technologies may also ascertain functional vision for improved pharmacotherapy. Less industrial scale-up may be owing to the pH sensitivity of phytosomes structure, which needs to be considered in their preparation by utilizing much more advanced and technological approaches. Factors which influence the phytosomes physicochemical stability should also be focused for the industrial production of these impressive nanocarriers. In future, industrial pharmaceutical companies may investigate newer opportunities for significant and potential developmental characteristics of phytosomes with suitably brilliant and well organized features.

CONCLUSIONS

Phytoconstituents generally possess poor absorption as well as low bioavailability, which ultimately reduce their therapeutic efficacy, due to which their utilization is confined. Therefore, phytoactive constituents combined with phospholipids in a stoichiometric ratio, complex thus formed has distinctive therapeutic advantages over conventional formulations. Phytophospholipid complex demonstrates significant as well as effective delivery of phytoconstituents. They boost the rate and extent of drug absorption by the oral and transdermal route. Phytosomes also reveal amazing and wonderful advantageous findings in the vistas of pharmaceuticals, cosmeceuticals and nutraceutical formulations. The information provided in this communication can be useful to explore newer avenues of phytosomes for technological advancements of useful phyto-molecules.

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Conflict of interest

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